REMARKS

Claims 1-9 are pending in the instant application.

Applicants have amended the specification to comply with the requirement that patent applications not contain embedded hyperlinks and/or other forms of browser-executable code as set forth in MPEP § 608.01. These amendments are supported in the specification as filed (see p. 28, line 29, to p. 29, line 11; p. 80, lines 4-12).

Applicants have amended Claims 1, 4, and 7 to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. In particular, Claims 1 and 4 have been amended to clarify the specific proteins used by the cell in the claimed screening method, and Claim 7 has been amended to clarify that the phosphothreonine substitution occurs at the threonine at position 8 of SEQ. ID. NO. 91, which is equivalent to the position of the phosphothreonine situated at position 187 relative to the p27 full-length sequence. Support for amended Claim 7 is found in the specification, which indicates that the threonine at position 8 of the sequence is phosphorylated (see p. 14, lines 23-26, and p. 91, lines 17-20).

As such, no new matter has been added by this amendment. Claims 1-9 will be pending upon entry of the instant amendment.

1. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner rejects Claims 1-9 under 35 U.S.C. § 112, second paragraph, for being indefinite. Applicants submit that the rejections have been obviated or overcome for the reasons set forth below.

First, the Examiner contends that the "metes and bounds of the activity of Skp2" as recited in Claims 1, 4, and 7 are not defined in the specification. Applicants submit that "the activity of Skp2" is not indefinite, but, rather, would be clearly understood by the skilled practitioner to refer to the well-defined Skp2 activities including the following: interaction with molecules involved in the cell cycle, interactions with cell cycle regulators, ubiquitination of Skp2-specific substrates, ubiquitin ligase, and substrate degradation activities (see p. 50, line 17, to p. 51, line 30). Numerous examples of such Skp2 activities are given in the specification. For example, the specification teaches that Skp2 associates

with Skp1, Cul-1, and ROC/Rbx1 to form the SCF^{Skp2} E3 ubiquitin ligase complex (see p. 3, lines 15-17). Moreover, the specification also teaches that Skp2 binds phosphorylated p27 and increases p27 ubiquitination and degradation (see p. 3, lines 14-15). In addition, Skp2 binds Cks1 to facilitate p27 ubiquitination and degradation (see p. 105, lines 19-26). As such, Applicants submit that, considering the teachings of the specification, including the numerous examples of the activity of Skp2, one of skill in the art would readily understand the metes and bounds of the term "activity of Skp2."

The Examiner also contends that Claim 7 is indefinite in the recitation of phosphothreonine at position 187. In response, Claim 7 has been amended to indicate that the phosphothreonine occurs at the threonine at position 8 of SEQ. ID. NO. 91. Support for this amendment is found in the specification, wherein the threonine at position 187 of the p27 gene is identified within the sequence comprising SEQ ID NO. 91 in Claim 7 (see p. 14, lines 23-26, and p. 91, lines 17-20). As such, Applicants believe that Claim 7, as amended, is not indefinite.

In view of the foregoing, Applicants submit that the rejection for indefiniteness under 35 U.S.C. §112, second paragraph, has been obviated and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The Examiner rejected Claims 1-9 as being obvious in view of Zhang *et al.* ("Zhang") combined with Lyapina *et al.* ("Lyapina"), Yu *et al.* ("Yu"), and Tsvetkov *et al.* ("Tsvetkov"). Applicants submit that the rejection is in error for the reasons set forth below.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. In re Vaeck 947 F.2d 488 (Fed. Cir. 1991).

The present invention relates to screening assays for compounds that alter the interaction of Skp2 and Cks1 or the interaction of Skp2, p27, and Cks1. The invention is based on the discovery by the inventor of a novel mediator of the SCF^{Skp2} ubiquitin ligase pathway, previously identified as a cyclin dependent kinase subunit, Cks1. In particular, the Applicant discovered that Cks1 interacts with both Skp2 and p27 to mediate the ubiquitination and degradation of the substrate p27. This novel interaction between Skp2, p27, and Cks1 was used to design novel assays to screen for compounds useful for the treatment of proliferative and differentiative disorders. Pending Claims 1-9 are specifically directed to such novel screening assays.

The references on which the Examiner relies for rejection of obviousness relate to interactions between Skp2, p27, and Cul-1, not Skp2, p27, and Cks1. These references therefore do not teach the methods of the present invention.

In Zhang, Skp1 and Skp2 are cloned, the Skp1/Skp2/cyclin A/CDK2 complex is identified, Skp2 is shown to be necessary for S-phase entry, and Skp2 expression is shown to be elevated in transformed cells and in S-phase. Zhang mentions that Cks1 is part of a complex with Skp1, Skp2, cyclin A, and CDK2; however, Zhang does not teach or suggest that such a complex has ubiquitin ligase activity, nor is there any suggestion that this complex might target p27 or affect p27 ubiquitination or degradation or that Cks1 is involved in mediating ubiquitination of p27 by interacting with both Skp2 and p27.

Yu describes interactions between Cul-1 and the Skp1/Skp2 complex. Yu describes the Skp1/Skp2/Cul-1 complex and its possible function as an E3 ligase to selectively target cyclin D and p21 for degradation. However, Yu does not teach a complex containing Skp2 and Cks1, and does not suggest that Skp2/Cks1 interactions would enhance p27 ubiquitination or degradation. (If anything, Yu in fact teaches away from the claims, by indicating that Skp2 ablation does not affect p27 degradation (see Yu, p. 11327)).

Lyapina and Tsvetkov also relate to interactions between Skp2 and Cul-1. Lyapina teaches that biochemical assays can be used to identify regulators of Cul-1 based SCF complexes for modulators of the Skp1 and Cul-1 proteins. However, Lyapina does not disclose complexes containing Cks1. Furthermore, the conclusion in Lyapina to which the Examiner points relates to Cul-1 and Skp1, not Cks1 or Skp2. Tsvetkov teaches the targeting of p27 by Skp2 for p27 degradation during cell cycle progression. However, Tsvetkov does not suggest any interactions between Cks1 and Skp2 in p27 ubiquitination or degradation.

Taken together, the combined references of Zhang, Yu, Lyapina, and Tsvetkov do not teach or make obvious the methods of the invention. Zhang mentions a complex containing Cks1 and Skp2 but does not suggest a direct interaction between Cks1 and Skp2, nor does Zhang suggest that complexes containing Cks1 and Skp2 would target p27 for ubiquitination or degradation. Yu, Lyapina, and Tsvetkov do not even discuss Cks1 or its interaction with Skp2 or p27. Thus, these references fail to suggest that assays comprising contacting a test compound with a cell or a cell extract expressing Cks1 and Skp2 or Cks1, p27 and Skp2, and detecting a change in the activity of Skp2, would lead to the discovery of compounds useful for the treatment of proliferative and differentiative disorders.

The rejection appears to be based on the Examiner's assumption that the human Cul-1 protein is the same as the Cks1 protein "as it exists in the same complex with Skp1 and Skp2" and "as it is part of the SCF ubiquitin ligase complex" controlling S-phase entrance, as detailed on page 5 of the Examiner's Office Action, which further states that the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. Applicants submit that the claimed Cks1 is distinct from Cul-1 referred to in the cited references.

Applicants assert that Cul-1 and Cks1 are different proteins, as described in the specification. For example, human Cks1 is a member of the Suc1/Cks (cyclin dependent kinase subunit) family of proteins (see p. 3, lines 22-27). Cks1 binds Skp2 and also binds phosphorylated p27 (see p. 97, lines 26-27, p. 105, line 27 to p. 106, line 9). Figure 46 shows identification of Cks1 as the factor required for ubiquitin ligation to p27. Figure 46B indicates that the protein fraction containing p27 ubiquitination activity migrates at approximately 10 kDa, identifying Cks1 as a small protein of approximately 10 kDa. On the other hand, Cul-1 is described in the specification as a member of the family of cullin proteins (see p. 3, lines 10-11, and p. 77, lines 17-19). Cul-1 is a part of the SCF^{Skp2} complex, along with Skp1, Skp2, and ROC/Rbx1 (see p. 3, lines 15-17, and p. 77. lines 17-24). Figure 30 indicates that Cul-1 migrates as a protein with a molecular weight of approximately 97 kDa. Thus, Cul-1 is a significantly larger protein than the 10 kDa Cks1, and is clearly not the claimed Cks1 product. The data presented in Figure 45C distinguishes Cul-1 from Cks1 in terms of activity, as it indicates that the SCF^{Skp2} complex containing Cul-1 still requires the factor from Fraction 1 (the factor from Fraction 1 being later identified as Cks1) for p27-ubiquitin ligation (p. 18, lines 5-6; p. 102, lines 7-32). As such, Cul-1 and Cks1 are clearly

distinct, and Applicants have therefore met their burden in proving that the novel interaction between Skp2 and Cks1, and/or Skp2, Cks1, and p27, is different from the prior art.

Therefore, the methods of the present invention are not made obvious in view of the prior art. In view of the foregoing, Applicants submit that the rejection for obviousness under 35 U.S.C. §103(a) should be withdrawn.

Finally, the Examiner's attention is directed to the Examiner's comment on page 3 of the Office Action, which states that this application currently names joint inventors. Applicants respectfully point out that this application names a single inventor, Michele Pagano, so the Examiner's concerns are deemed not applicable to the claims of the instant invention.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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